BASE-INDUCED REACTIONS OF N-METHYL QUATERNARY SALTS OF 1-AZA-DIBENZO[c,f]BICYCLO[3.3.1]NONA-3,6-DIENE AND RELATED COMPOUNDS

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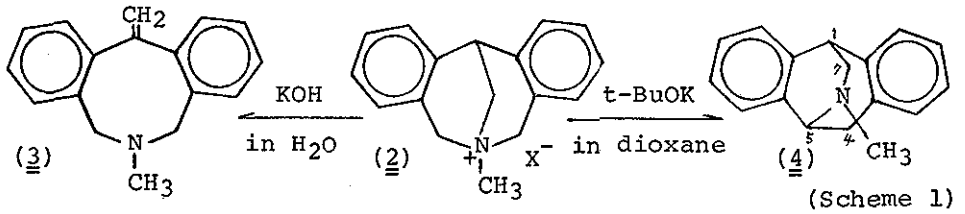
Reactions of N-methyl quaternary salt (2) of 1-azadibenzo[c,f]-bicyclo[3.3.1]nona-3,6-diene (1) with various bases were examined, and consequently, 6-aza-6-methyldibenzo[b,i]bicyclo[3.2.2]nona-2,8-diene (4) was selectively obtained by the reaction of 2 with potassium t-butoxide in dioxane, in contrast 1-aza-1-methyl-5-methylene-dibenzo[c,f]octa-3,6-diene (3) was provided as a sole product by the reaction with potassium hydroxide in water, respectively. Isopavine alkaloids, (±)-amurensinine and (±)-reframine were also derived.

Previously, we reported[1] that N-methyl quaternary salts (2, X=OH) of 1-azadibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene (1), which was facilely synthesized in high yield by the double-cyclization reaction of N,N-dibenzylaminoacetaldehyde diethylacetal, was derived to pharmacologically active 1-azadibenzo[c,f]octa-3,6-diene derivative (3) by thermal degradation. In the course of our studies

on the ring transformation of 1, we here wish to describe that 2 was converted into a basic skeleton of the isopavine alkaloids[2], namely, 6-aza-6-methyldibenzo[b,i]bicyclo[3.2.2]nona-2,8-diene (4)[3] in high isolated yield, by employing strong bases such as n-BuLi, t-BuOK, and NaH in rather aprotic solvents, whereas 3 was provided as a sole product by the reaction of 2(X=CH_3SO_4) with a large excess of KOH in water at refluxing temperature(Scheme 1, Table I).



(3) (2) (4)

(Scheme 1)

Table I Reactions of N-Methyl Quaternary Salts (2) with Bases

2: X	Base*b	Solvent	Temp(°C)	Time(hr)	Yield(%)*d 3	4
OH*a	none	none	180	1/4	28	38
CH_3SO_4	KOH*c	water	100	14	55	0
CH_3SO_4	KOH*c	water/diglyme (1:2.5)	150	3	1	50
I	n-BuLi	ether	-78~r.t.	16	0	66
I	t-BuOK	dioxane	r.t.	42	3	64
I	t-BuOK	diglyme	180	2/3	2	76
I	t-BuOK	dioxane	80	4	1	85
I	NaH	diglyme	180	1	0	81

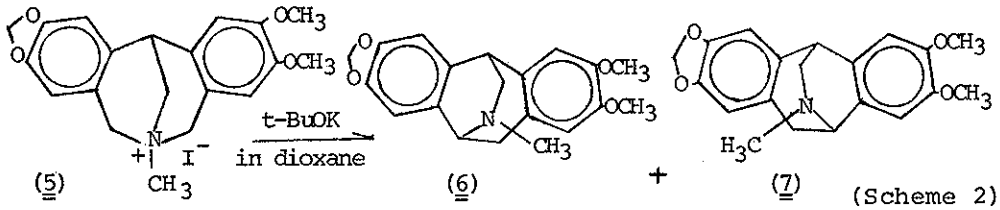
*a) See references 1). *b) 1.5 equiv. to 2. *c) 50 equiv. to 2.
*d) The isolated yield shown was unoptimized.

In a typical experiment, compound 2(X=I)(1 mmol) in a solution of dioxane containing 1.5 equiv. of t-BuOK, was heated with stirring at 80°C for 4 hr under an argon atmosphere. After dilution

with water, the reaction mixture was extracted with dichloromethane and the resulting solution was evaporated under a reduced pressure, the residue was chromatographed on a silica gel column affording 4, mp 60-62°C, in 85% yield. 4: Mass m/e 235(M^+), 192 (M-(CH_3-N=CH_2)), 144(N-methylisoquinolinium ion)[4], ^{1}H-NMR(δ in $CDCl_3$) 2.44(3H,s), 2.86(1H,dd,J=10.6, 5.0Hz), 2.94(1H,dd,J=17.5, 1.25Hz), 3.54(1H,dd,J=10.6, 1.25Hz), 3.58(1H,dd,J=17.5, 3.75Hz), 3.79(1H,dd,J=5.0, 1.25Hz), 3.89(1H,t,J=3.75Hz), ^{13}C-NMR(δ in $CDCl_3$) 38.5(C_4,t), 45.3(N-$\underline{C}H_3$,q), 46.9(C_1,d),59.6(C_7,t),62.6(C_5,d).

In an application of this modified Stevens rearrangement[5], 5, prepared by the double-cyclization reaction of N-(3,4-dimethoxybenzyl)-N-(3,4-methylenedioxybenzyl)aminoacetaldehyde diethylacetal, in a dioxane solution containing 1.5 equiv. of t-BuOK was heated at 80°C for 4 hr and chromatographic separation gave (±)-amurensinine (6) and (±)-reframine (7) in 85% yield(1.8:1). 6:[6] mp 192-194°C, Mass m/e 339(M^+), 296(M-(CH_3-N=CH_2)), 188(N-methyl-6,7-methylenedioxyisoquinolinium ion)[4], NMR(δ in $CDCl_3$) 2.48(3H, s), 2.70-3.04(2H,m), 3.36-3.70(4H,m), 3.77(3H,s), 3.86(3H,s), 5.85 (2H,ABq,J=4.0, 1.5Hz), 6.48(1H,s), 6.58(1H,s), 6.65(2H,s). 7:[7] oil(methiodide, mp 262-263°C), Mass m/e 339(M^+), 296(M-(CH_3-N=CH_2)), 204(N-methyl-6,7-dimethoxyisoquinolium ion)[4], NMR(δ in $CDCl_3$) 2.47 (3H,s), 2.8-3.04(2H,m), 3.44-3.80(4H,m), 3.86(6H,s), 5.85(2H,ABq, J=2.5, 1.0Hz), 6.45(1H,s), 6.59(1H,s), 6.68(1H,s), 6.71(1H,s). The spectroscopic data of the available natural products were identical with those of 6 and 7 respectively (Scheme 2).

In conclusion, the presented results suggest clearly that pharmacologically active type-3 and type-4 compounds can be selec-



(5) (6) + (7) (Scheme 2)

tively synthesized from type-1 compounds.

Further studies along this line and the investigation on the reaction mechanism are in progress.

References and Notes

1) H. Takayama, M. Takamoto, and T. Okamoto, Tetrahedron Lett., 1978, 1307. The crystalline 2(X=CH_3SO_4) was dissolved in H_2O and passed through OH^--treated IRA-401 ion exchange column and the resultant aq. solution was concentrated to dryness under a reduced pressure at below 30°C, followed by a vacuum distillation (oil bath temp. 180°C/0.005 Torr) affording a mixture of 3(28%) and 4(38%). The yields were sensitive to the reaction procedure.

2) S. F. Dyke and A. C. Ellis, Tetrahedron, 1971, 27, 3803 and the references cited therein.

3) 4 displayed various interesting pharmacological activities (unpublished result).

4) L. Dolejš and V. Hanuš, Coll. Czech. Chem. Commun., 1968, 33, 600 ; L. Dolejš and J. Slavík, ibid., 1968, 33, 3917.

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6) F. Šantavý, L. Hruban, and M. Maturová, Coll. Czech. Chem. Commun., 1966, 31, 4286 ; Idem, J. Chem. Soc. Chem. Commun., 1966, 36.

7) J. Slavík, L. Slavíková, and L. Dolejš, Coll. Czech. Chem. Commun., 1968, 33, 4066.

8) Compounds 3, 4, 6, and 7 (methiodide) gave correct elemental analyses.

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